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Apparent Solubility of Drugs in Partially Crystalline Systems

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ABSTRACT

Using several griseofulvin samples, representing different solid-state structures, the solubility behavior of drugs in both one-state (totally ordered, semiordered or disordered) and two-state systems was studied. Special attention was directed towards the surface structure of the particles. The partially crystalline samples were obtained by milling the raw material (crystalline standard) or storing the quenched sample (amorphous standard). The solid-state structure of the materials was studied using x-ray diffraction (XRD), differential scanning calorimetry (DSC), isothermal microcalorimetry (IMC), and scanning electron microscopy (SEM). The saturation concentration of the materials was studied in suspensions containing different dispersion concentrations of drug after centrifugation and filtration, using spectrophotometry. In all cases these dispersion concentrations exceeded the solubility of the drug. The solubilities were plotted vs. dispersion concentrations for each sample. Several solubility plateaus were found. The lowest and highest solubility plateaus corresponded to the solubilities of crystalline and amorphous standards. These plateaus were reached at 8 and 44 μg/mL for crystalline and amorphous griseofulvin standards, respectively. An intermediate plateau served as an indication of the existence of a totally semiordered structure. This was reached at 19 μg/mL for griseofulvin. Any deviation from these plateaus was suggested to be indicative of the existence of heterogeneity on the surface structure, which in most cases could be described as a two state system. In such cases, the apparent solubility was a function of dispersion concentration, until at very high dispersion concentrations (4000–20,000 μg/mL) the saturation concentration of the totally disordered (44 μg/mL) or semiordered (19 μg/mL) one-state phase was reached. No reduction in these values was observed during storage for 50 days. It is thus concluded that, in partially crystalline systems, the saturation concentration is an interfacial phenomenon, which depends on the amount, reactivity, and solid-state structure of the exposed solid surfaces in equilibrium with the solution. A simplified solubility model is proposed to qualitatively describe the relationship between

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established apparent solubilities (saturation concentrations) and different combinations of solid-state structures.

Key Words: Solid-state structure; Partially crystalline; Semiordered; Mechanical activation; Quenching; Apparent solubility; Dispersion concentration; Plateau value; Metastable.

INTRODUCTION

Solid-state disorder (amorphous character) may be induced in a solid by altering the crystallization conditions or subjecting the solid to mechanical forces. In many cases, it has been reported that the resulting solid particles are partially crystalline (partially amorphous). For instance, it has frequently been reported that solid forms, which differ in the degree of disorder, have been obtained after spray drying,[1–3] freeze drying,[4] and quenching.[5]

Further, it is well-known that mechanical treatment of a crystal (such as milling) often leads to surface activation, lattice disorder, and formation of partially amorphous solids.[6–7] Shalaev et al.[8] reported that in addition to creating an amorphous phase with greatly enhanced disorder, processing could increase the extent of disorder in the remaining crystal lattice. Furthermore, they claimed that such processes produce different extents and types of disorder, e.g., different concentrations of points, linear defects (dislocations), and planar defects.

Conversely, during processing[9] or storage[10,11] of an amorphous material, the amorphous state may be converted back to the crystalline state. The latter effect is related to the higher reactivity[8] of the amorphous region compared to crystalline materials. This high reactivity increases the tendency for amorphous material to react with environmental moisture,[12] to degrade,[13] or to take part in solid-state reactions[14] during storage. Numerous reports have thus concluded that solids can exist in rather complex structures, far from an ideal crystalline state, but also far from a totally amorphous, disordered structure. The term ''partially crystalline systems'' is often used to collectively denominate such complex structures.

Partially crystalline systems have been described using either one-state or two-state models.[11] According to the two-state model, solids are either crystalline or amorphous, or a mixture of the two. The expression degree of disorder will then refer to the fraction of amorphous material in the mixture.[15] An alternative concept is that the degree of disorder has a value between 0% (perfect crystal) and 100% (amorphous) depending on the ratio of disorder/order in the lattice.[16] This is called the one-state model. According to Hancock and Zografi,[11] the solid-state structure of a partially crystalline system in the one-state model ''consists of domains which are truly partially crystalline and in which the molecules have formed a semi ordered structure as a result of being restricted in their motion during crystallization, or following the disruption of a more perfect crystalline state.''

Similarly, other authors have interpreted the variations in solid-state structure, and the related physicochemical properties obtained after spray drying, to the existence of different amorphous structures[3] or the creation of different amorphous spray-dried products when the drug is complexed with different amounts of polyvinyl pyrrolidone (PVP).[1] These workers have reported an accompanying change in the glass transition temperature (T_g). Additionally, the existence of multiple metastable glasses below T_g, and even polyamorphic glasses, has been presumed.[11] These reports indicate that just as there are different polymorphs for a crystalline structure, there are also different forms of disordered/semiordered structures of a material that vary in the degree of disorder and in physico-chemical properties such as solubility.

To summarize some of the potential activation-deactivation processes and phase transitions from crystalline to amorphous structure (and vice versa) through formation of partially crystalline intermediates, Fig. 1 is used as a simplified illustration. In this model both one-state and two-state systems are considered and utilized.

The existence of partially crystalline structures is of special importance at solid interfaces. Since apparent solubility and initial dissolution rate are both related to the interfacial properties of the drug particles, it is of major importance to study the effect of surface structure on these parameters. Improvement in the solubility of drugs after spray drying,[17] freeze drying,[4] the preparation of solid dispersions,[18] milling,[19–21] and dry mixing[22] have been reported to be related to a change in the solid-state structure of the material, usually from a more ordered to a less

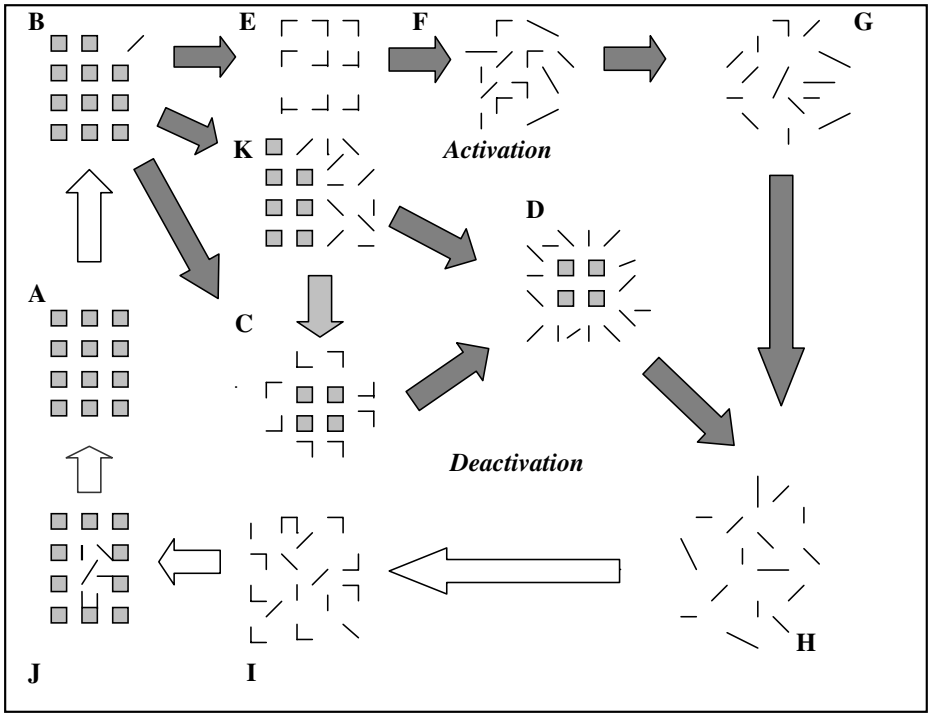

Figure 1. Activation and deactivation processes and the phase transition from a totally ordered structure (A) to a totally disordered structure (H) and vice versa. In this figure, polymorphic conversions that might occur between A and C are not illustrated. Symbols: ■, ordered; ⫠, semiordered; and //\\, disordered. (A) Totally ordered structure; (B) Totally ordered with minor amounts of impurities or defects; (C) Semiordered surface, ordered core; (D) Disordered surface, ordered core; (E) Totally semiordered structure; (F) Semiordered structure with a more disordered character (assuming one-state model); (G) Semiordered structure with a much more disordered character (assuming one-state model); (H) Totally disordered structure; (I) Semiordered surface, disordered core; (J) Ordered surface, disordered core; (K) Solid in which the totally ordered and totally disordered parts coexist (a two-component state, i.e., the structure is not semiordered).

ordered structure. It is also generally accepted that the surface of milled particles becomes increasingly more energetic as indicated by a higher surface energy[23–25] and a larger electron-donating capacity.[25]

From the above discussion it can be concluded that if a solid particle consists of structural composites of varying molecular order, then the solid surface of the particle could be in four main states: 1) the surface could be homogeneously, completely ordered, 2) the surface could be homogeneously, completely disordered, 3) the surface could be homogeneously disordered, but not completely (i.e., semiordered, with a partially ordered molecular orientation), 4) the surface could be a heterogeneous mixture of more ordered and less ordered phases. It should be noted that in the latter case, the energy state of the disordered parts may also vary. Cases 1, 2, and 3 are based on the one-state model and case 4 is based on the two-state model.

Before discussing the apparent solubility of partially crystalline systems, it is important to define the terms "saturation concentration," "solubility," and "apparent solubility."

When an excess amount of solid is inserted into solvent, under defined temperature and after sufficient stirring time, equilibrium is established between the solid surface and the surrounding solvent. Under such circumstances, the solvent is saturated with solute and the concentration of solute is called the saturation concentration. In the literature the term "saturation concentration" (Cs) is often exchangeable with "solubility." However it should be pointed out that the latter refers to equilibrium between the solid and solvent, when the solid is in its most thermodynamically favored form (i.e., crystalline). It is also known that in a metastable or supersaturated solution, the amount of dissolved solute may be initially high and then reduced to the thermodynamically stable value over time. The time it takes for such

a reduction in concentration depends on several factors and could vary between seconds to months. Since most of the reports in this field deal with those cases where the systems are very unstable, the importance of such relative equilibrium conditions has not been emphasized. In the present study, since the obtained saturation concentrations are much greater than the thermodynamically stable values reported in the literature as solubility, and also are quite stable over a period of time (months), the term ''apparent solubility'' is applied. The term ''apparent solubility'' is thus used throughout this article for the metastable or dynamic solubility of the materials rather than the solubility, which refers to a thermodynamically stable state.

It has been reported[20,21] that if the particle surface is disordered to some degree, the apparent solubility will be a function of the amount of drug dispersed in the medium. In such cases, the dispersion concentration will determine the amount of disordered surface area present in the medium, emphasizing the critical role of available disordered surface area for dissolution. Under such circumstances, the saturation concentration is increased as the amount of drug added is increased, until finally at higher additions it reaches a plateau. In an attempt to elucidate this matter, a schematic model was proposed by Mosharraf, Sebhatu, and Nyström.[21] It was assumed that in a plot of apparent solubility vs. the dispersion concentration of the solid drug, there are several possible plateau levels for every substance. The level of the plateau is determined by the solid-state structure of the material. In the model, the lowest plateau level would correspond to the solubility of the purely crystalline form and the highest plateau level would correspond to the solubility of the totally disordered form. The solubility plateau of particles with a partially crystalline surface would be intermediate. The following outcomes were suggested on the basis of this model: 1) The solubility of totally ordered and totally disordered solids is in principle independent of the dispersion concentration of the solid in suspension, and two distinguishable saturation levels will be established; 2) If the particle surface is disordered as a continuous layer, and the concentration of the drug in the solvent is high enough, the solubility plateau will be determined solely by the disordered phase and will approach that seen for a totally amorphous drug structure; 3) If the particle surface is partly crystalline and partly amorphous (assuming a two-state model), some areas of crystalline structure will be exposed even if high amounts of drug are added, and the solubility plateau will be intermediate between those of the purely crystalline and the purely amorphous states. The solution will be simultaneously in equilibrium with the crystalline and disordered surfaces. Thus the net equilibrium between the medium and these surfaces will determine the solubility of the drug.

The duration of the period of increased (metastable) solubility is generally thought to be controlled by the rate of nucleation and, thus, the rate of growth of the more stable phase.[26] Many researchers have based their data analysis on the assumption that the processes of dissolution of the metastable form and crystallization of the stable form are both diffusion controlled. The surface area available for growth and the stirring rate of the system would then be rate-determining factors for the transformation process to the stable, crystalline form. For example, according to Cardew and Davey,[27] the time required for disappearance of the metastable phase is the sum of dissolution and growth time scales. The plateau supersaturation will then be the point at which dissolution and growth are balanced. Its value is determined by the relative surface areas of the phases and their kinetic constants. Rodriguez-Hornedo, Lechuga-Ballesteros, and Wu,[28] however, suggested that polymorphic phase transformations are dependent on supersaturation of the solvent and are independent of the stirring rate. They discuss the mechanisms behind the phase-transition process, i.e., transformation in the solid state. The results recently reported by Elamin et al.,[20] on the transformation of disordered griseofulvin to the crystalline form support the latter; i.e., transformation in the solid state.

In this study (20) and other studies (21) it has been shown that the apparent solubility of calcium carbonate and griseofulvin has been stable in both stirred and unstirred systems up to several days, suggesting that the recrystallization rate of these materials is controlled by a surface solid-state transformation mechanism.

AIM

The aim of this study was to continue the investigation of the solubility of partially crystalline systems, and especially to study (using knowledge of the amorphous content of the test materials) the validity of the solubility model described by Mosharraf, Sebhatu, and Nyström[21] and the possibility of using this model for detection of minor amounts of surface disorder in the solid-state structure of drugs.

MATERIALS

Three forms of the test drug, griseofulvin, were used: crystalline, partially crystalline, and amorphous. These were studied as seven samples, which are described in Table 1.

The dissolution medium consisted of ultra pure particle-free water (Milli Q UF Plus, Sundbyberg, Sweden) containing 0.9% NaCl and 0.01% Tween 80.

METHODS

Sample Preparation

The raw material (griseofulvin microsized crystals, Glaxo, Greenford, Middlesex, England) was used to represent a totally crystalline sample as discussed below.

The raw material was milled in a mortar grinder (mortar grinder, type KMI, Retsh GmBH, Haan, Germany) for 1.3 min (RM1) and 3.4 min (RM2), in order to create an activated (possibly amorphous) surface on the crystalline particles.

The disordered samples were prepared by quenching the raw material. Two batches of quenched griseofulvin were prepared (Q1 and Q2). In both cases the raw material was melted in aluminium foil over heat. The melt was then immediately immersed into liquid nitrogen for rapid cooling and solidification (quenching). The quenching procedure was the same in both cases except that in the case of Q1, the griseofulvin was heated for a longer period of time (approximately one min more) and the melt was solidified faster than with Q2.

In order to deactivate the disordered surface of quenched griseofulvin (Q1) by recrystallization due to moisture uptake, the sample was stored under ambient conditions ($22^{\circ}C \pm 1$ and 40% RH) for 9 months. This sample was then called Q1S.

The Q1S sample was mechanically disintegrated (milled) with a mortar and a pestle for about 1 min to increase the amount of exposed amorphous surface area. This sample was called $Q1S_{milled}$.

Physical Mixtures of Crystalline and Amorphous Materials

In an attempt to investigate the apparent solubility of drugs in two-state systems, different proportions of amorphous (Q1S) and crystalline (raw material) griseofulvin were weighed in volumetric flasks. The total dispersion concentration was constant at approximately 4000 mg/L in all flasks. The ratios of griseofulvin crystals to Q1S particles were 100:0, 98:2, 50:50, 2:98, and 0:100% w/w. Since the degree of disorder in Q1S was assessed as 83% (see results below), the final proportions of disorder in the respective systems were calculated to be 0% (solely griseofulvin crystals), 5%, 43%, 79%, and 83% (solely Q1S particles) w/w. The apparent solubility of griseofulvin was then tested in each case after 3 hours and 24 hours of stirring. Each value is the mean of at least two experiments.

Particle Size and Shape

In order to estimate the particle size, shape, and surface texture, the samples were scanned in a JEOL JSM-T330 scanning electron microscope, using an acceleration voltage of 15 kV. In addition, the geometric mean particle diameter by weight ($n = 2$) of $Q1S_{milled}$ was determined by laser diffraction analysis (LS 230, Coulter, VWR International, Stockholm, Sweden) and compared with that of the crystalline material. The mean particle size data of the griseofulvin crystals were obtained from an earlier study using this batch.[29]

Table 1. Material description.

Material	Description	Color
R	Raw material (griseofulvin microsized crystals, Glaxo, UK)	White
RM1	Raw material after 1.3 min milling	White
RM2	Raw material after 3.4 min milling	White
Q1	Quenched griseofulvin 1 (longer heating time, faster solidification)	Glassy, brownish yellow
Q1S	Quenched griseofulvin 1, Q1 stored for 9 months under ambient conditions	Matte, light brownish yellow
$Q1S_{milled}$	Stored quenched griseofulvin (Q1S) after 1 min milling	Glassy, light brownish yellow
Q2	Quenched griseofulvin 2 (shorter heating time and slower solidification)	Glassy, light brownish yellow

Characterization of the Solid-State Structure

X-ray Diffraction (XRD)

In order to study the solid-state structure of the test materials, diffraction patterns of quenched (Q1, Q1S, and Q2) and raw materials were obtained using a Philips X'pert MPD diffractometer, with Cu Kα radiation at 40 kV and 50 mA. The samples were scanned in steps of 0.02° from 1–37° (2O) at a rate of 1 second per step. Each pattern is based on a single measurement.

Differential Scanning Calorimetry (DSC)

The thermal behavior of the samples was tested in a differential scanning calorimeter (Mettler TC 3000, Hightstown, NJ, USA) using sealed aluminum pans. About 4–5 mg of each sample was scanned at a temperature range of 25–250°C with a heating rate of 10°C/min. An empty sealed pan was used as the reference. Each value is the mean of two experiments. In the case of Q1, the results are based on a single experiment.

Glass transition temperature (T_g), recrystallization temperatures (T_c), and melting temperatures (T_m) were recorded. The enthalpies of crystallization (ΔH_c) and fusion (ΔH_f) were calculated by integrating the corresponding peaks in each case. These values were normalized for the eventual differences in sample weight.

The degree of disorder was then calculated by dividing the normalized ΔH_c value of the sample by that of the 100% amorphous standard (i.e., Q1).[30] As there were no recrystallization exotherms detectable by DSC for RM1, the degree of order was estimated from ΔH_f values[31,32] by dividing the ΔH_f value of RM1 by that of the 100% crystalline standard (raw material). Subtraction of this value from 100 would then give the degree of disorder (as %) in the material.

Isothermal Microcalorimetry (IMC)

These experiments were performed in a 2277 Thermal Activity Monitor (TAM) (Thermometric AB, Järfålla, Sweden). A 30 mg griseofulvin sample was weighed accurately into a glass vial. The samples were checked for the degree of disorder by exposing them to HCl vapor in the microcalorimeter. A small tube containing 1 M HCl was placed into the vial and the vial was sealed. As the materials tested in this study were sparingly soluble in water and hydrophobic, HCl was used instead of the salt solutions used by Angberg, Nyström, and Castensson[33] and ethanol, which was used by Ahmed, Buckton, and Rawlins.[34] All measurements were performed at 25°C. An empty, freshly sealed vial was used as the reference. The vial and the reference were equilibrated in the TAM before starting the experiment. The heat flow signal (dQ/dt in μw) was monitored as a function of time.

Color Shift

As it is known that color shifts in a powder may be related to polymorphic conversions and differences in molecular conformation,[35] the appearance and colors of griseofulvin samples were also compared.

Determination of Saturation Concentration

The apparent solubility of the test materials was studied in suspensions containing different dispersion concentrations (20 to 22,300 mg/L) of drug. The suspensions were stirred on a magnetic stirring board for 24 hours at a constant rate, at room temperature (22 ± 1°C). The supernatants were separated by centrifugation at a speed of 10,000 rpm, at 23°C for 10 min, using an Eppendorf 4403 (Bergman & Beving, Upplands Väsby, Sweden) centrifuge. They were then filtered through a 0.65 μm Millipore filter prior to concentration determination. The concentrations of griseofulvin were then assayed spectrophotometrically (Hitachi U-1100, Tokyo, Japan) at a wavelength of 295 nm. Each value is the mean of at least two experiments.

Stability of Obtained Solutions

After determination of the solubility, the stability of the solutions was tested. The supernatants obtained from Q1S suspensions (dispersion concentration in the range of 1200–4200 mg/L) were stored under ambient conditions for 50 days. These solutions were not exposed to any stirring during this period. At specific time intervals, the stored solutions were filtered through a 0.65 μm Millipore filter and the concentration of griseofulvin was determined

spectrophotometrically as described above. Each value is the mean of three readings.

RESULTS AND DISCUSSIONS

Particle Size and Shape

Typical SEM photomicrographs of quenched griseofulvin particles Q1S, $Q1S_{milled}$, and Q2 are shown in Figs. 2–3. The quenched samples Q1S and Q2 consisted of large (about 0.5–2 mm) lumps (Figs. 2a and 3a). However, in general, Q2 particles were smaller than Q1S particles and were less polydispersed. The surfaces of both Q1S and Q2 samples appeared to be covered with needle-like formations (Figs. 2b and 3b), possibly formed by dendritic growth and dendrite coarsening, which has been reported to occur at high supersaturation concentrations.[36] This external thin layer of dendrites or needlelike crystals did not cover the particle surface completely. When the internal structure of Q1S was scanned (Fig. 2c), however, there were no needlelike structures. The solid in this case had no fixed shape.

The particles in the $Q1S_{milled}$ sample were smaller than in the other samples (Fig. 2d). The proportion of needlelike crystals on the solid surface was also lower. The geometric mean particle diameter by weight of $Q1S_{milled}$ was determined using a laser diffraction technique as 4.8 μm. The griseofulvin crystals had a geometric mean particle diameter by weight of 3.7 μm, as measured by the Coulter principle.[29] Although there were no SEM photomicrographs

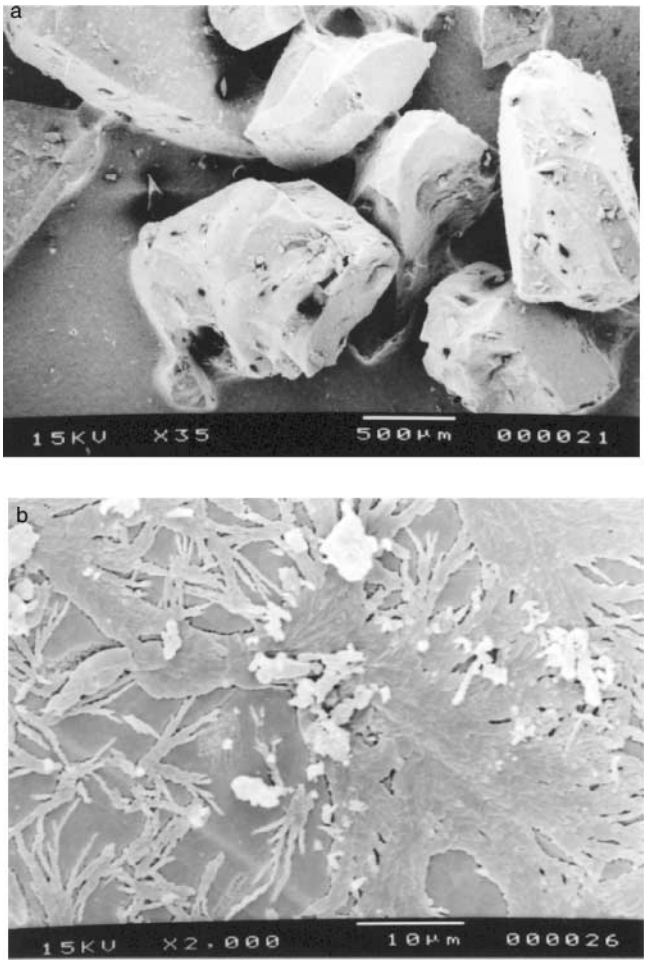

Figure 2. SEM photomicrographs of quenched griseofulvin Q1 after 9 months storage, i.e., Q1S: (a) Representative particles of Q1S, (b) the external surface texture and needlelike formations on the surface, (c) the internal particle morphology obtained by scanning the Q1S core in a particle slice, and (d) after size reduction and attrition ($Q1S_{milled}$).

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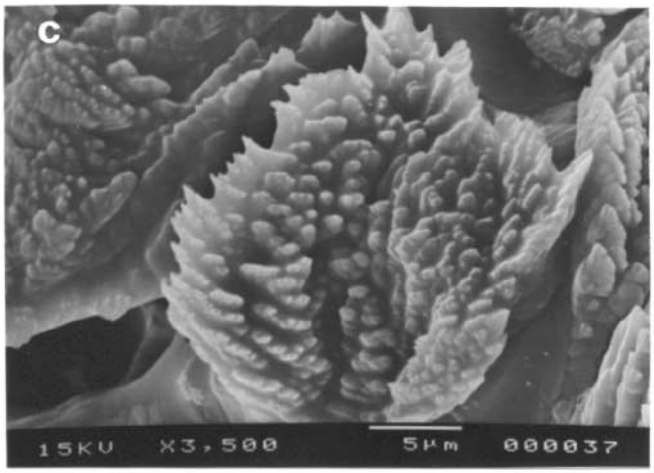

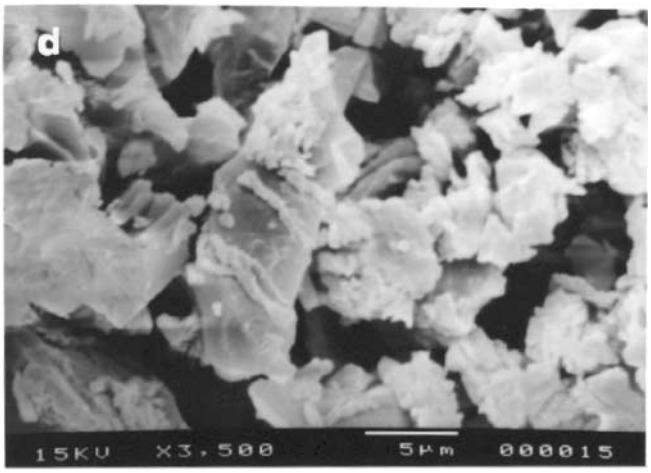

Figure 2. Continued.

available for the Q1 particles, macroscopic examination of these particles suggested a similar particle size to Q1S particles.

Assessment of Degree of Disorder

It is usually difficult to determine the degree of disorder quantitatively, especially only from the results of one method. Therefore in the present study the degree of disorder was estimated by comparison of results obtained from several methods.

The values for enthalpy of crystallization and melting obtained from DSC, and the heat flow values obtained from IMC, are listed in Table 2. The degree of disorder of the test materials was calculated using these values and is summarized in Table 3. The raw material and Q1 were used as crystalline and totally amorphous standards, respectively; this was supported by the data obtained by XRPD, DSC, and IMC (Figs. 4–6 and Tables 2–4).

In order to determine whether the observed peak in IMC reflects a chemical reaction with HCl vapor or a recrystallization due to exposure to HCl vapor, the quenched griseofulvin (Q1S) was tested in DSC, before and after exposure to HCl vapor in the microcalorimeter. The results showed that when the sample was removed from the microcalorimeter and scanned by DSC, there was no evidence for any recrystallization event, revealing that the solid-state structure of the sample had changed due to exposure to HCl vapor. Thus, as a general conclusion, the heat evolved was interpreted as a phase-transition event. The heat evolved or absorbed (Q in J) was calculated by inte-

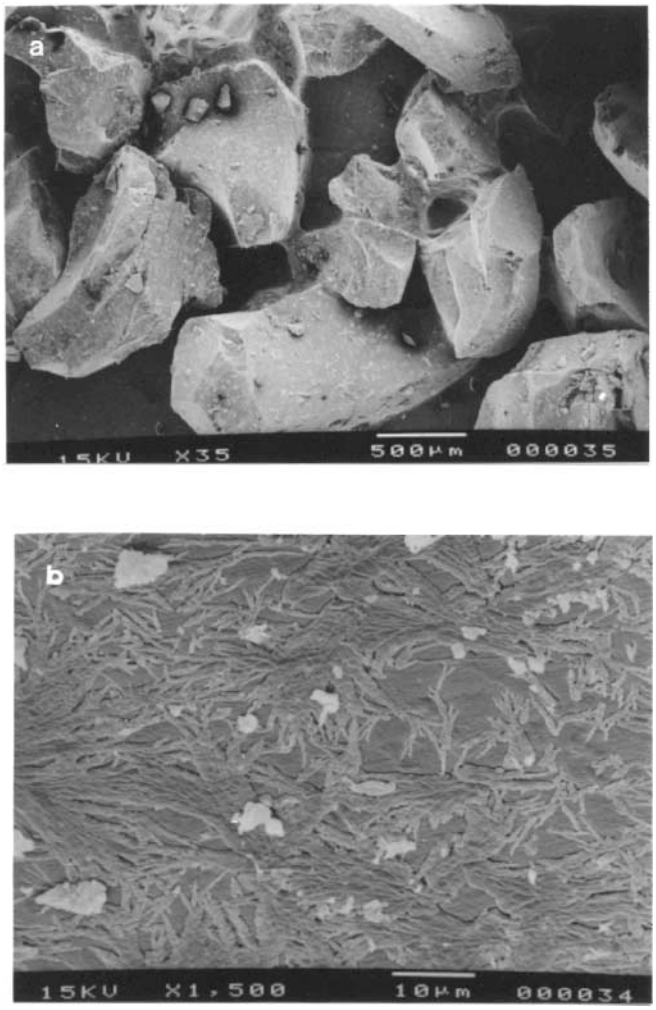

Figure 3. SEM photomicrographs of quenched griseofulvin, Q2: (a) Representative particles of Q2, (b) the external surface texture and needlelike formations on the surface.

Table 2. DSC and IMC data.

	Glass transition temperature T_g (°C)		Recrystallization temperature T_c (°C)		Melting point T_m (°C)	Heat of crystallization ΔH_c	Heat of fusion ΔH_f	Heat of relaxation ΔH_r	Heat flow Q
Material	Onset	Peak	Onset	Peak	Peak	(J/g)	(J/g)	(J/g)	(J/g)
R	—	—	—	—	220	—	122.0	—	0
RM1	—	—	—	—	221	—	119.0	—	2.87
RM2	—	—	—	—	—	—	—	—	0.72
Q1	90	—	133	138	220	83.0	104.7	—	—
Q1S	77	81	123	125	220	69.8	98.6	3.9	44.7
$Q1S_{milled}$	76	85	113	126	218	58.2	101.3	4.2	46.0
Q2	89	—	127	136	220	78.1	111.7	—	43.5

grating the heat flow curve.[30] The degree of disorder was calculated by comparing the area under the exothermic peak to that of the amorphous standard (the values were normalized for eventual weight differences). Since Q1 converted to Q1S on storage, there was no access to Q1 during IMC measurements. However, since the degree of disorder in Q1S was known and assessed to be 83% by DSC, this sample was used as the reference in calculation of degree of disorder in Q2, $Q1S_{milled}$, RM1, and RM2. Each value is the mean of two experiments. In the case of $Q1S_{milled}$, the result is based on a single experiment.

Table 3. Qualitative estimation of degree of disorder.

	Degree of disorder (%)		
Materials	XRDP	DSC[a]	IMC[c]
R	0	0	0
RM1	—	2.5[b]	5.3
RM2	—	—	1.3
Q1	100	100	—
Q1S	90–95	83	83[d]
$Q1S_{milled}$	—	67	85
Q2	100	94	81

[a]The degree of disorder was calculated from: $(\Delta H_{c(sample)}/\Delta H_{c\ (QI)}) \times 100$.
[b]The degree of disorder was calculated from: $100 - [(\Delta H_{f\ (sample)}/\Delta H_{f(Q)}) \times 100]$.
[c]The degree of disorder was obtained from: $(Q_{(sample)} \times 100)/Q_{(QII)}$.
[d]This value is based on the DSC measurements.
The enthalpy ΔH) and heat flow (Q) values used in these calculations are taken from Table 1.

The Effect of Milling on the Solid-State Structure and Saturation Concentration of Griseofulvin Crystals

After milling, the powder did not change its color (Table 1), but a small degree of disorder was detected by DSC and IMC (Table 3). The difference in the estimated degree of disorder by these methods might be explained by the lower sensitivity of DSC in detecting small amounts of disorder compared with IMC, since thermal analysis did not easily identify changes that take place at a particle surface for only a few nanometers into the crystal.[37]

These results correlate fairly well with the solubility data, and as shown in Fig. 7, the apparent solubility was increased significantly after milling.

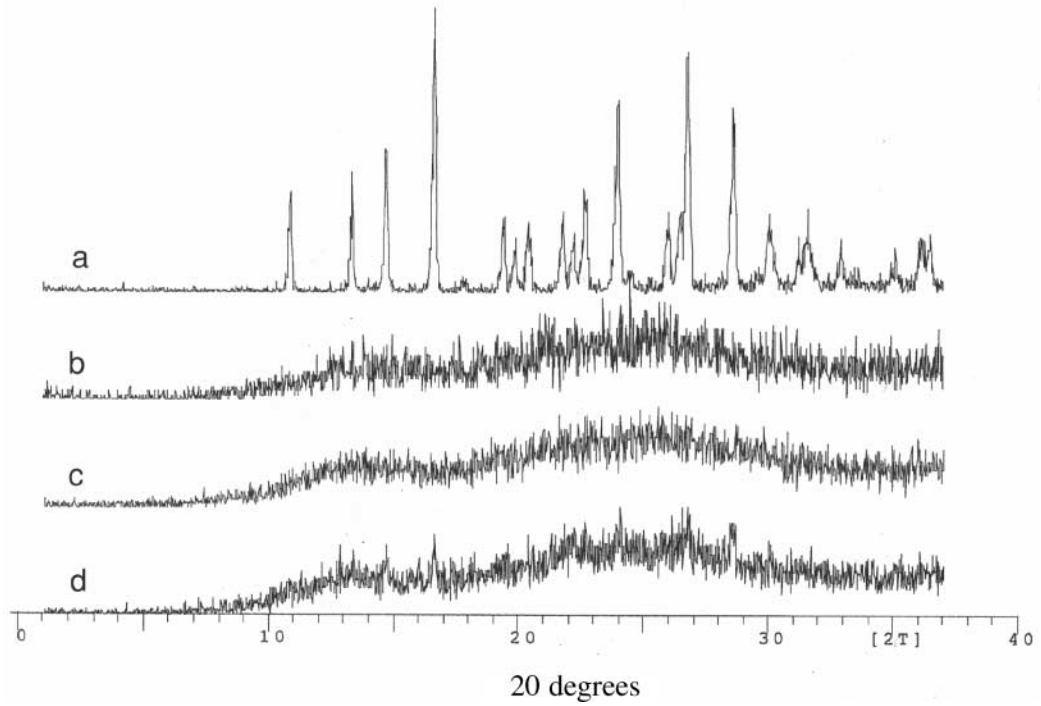

Figure 4. XRPD patterns of griseofulvin samples: (a) raw material, R, (b) quenched sample, Q1, (c) quenched sample, Q2, and (d) Q1 after 9 months storage under ambient conditions, Q1S.

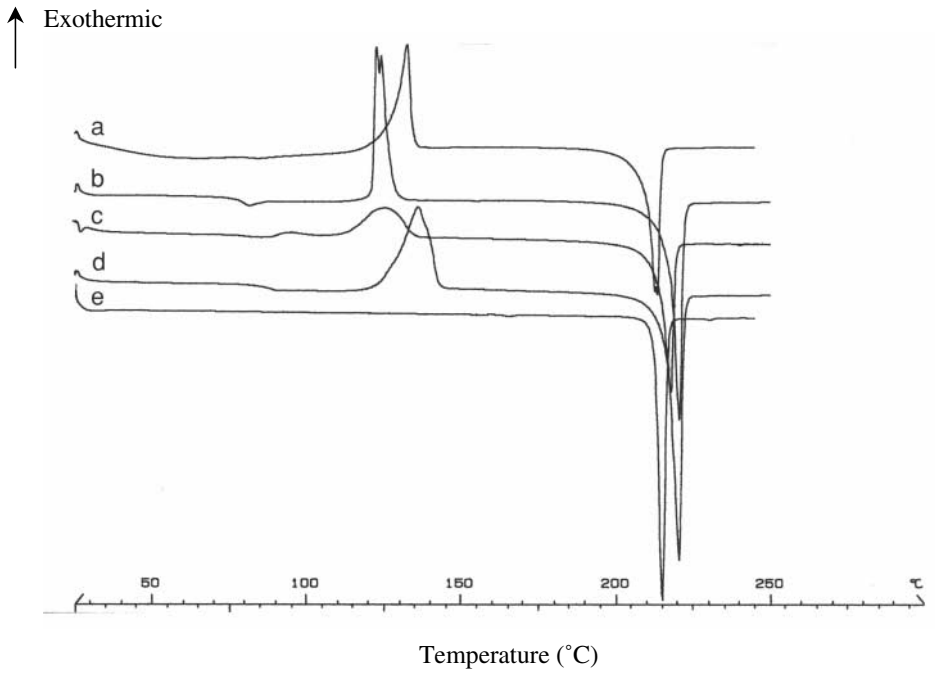

Figure 5. DSC scans of griseofulvin samples: (a) quenched griseofulvin reference, Q1, (b) Q1 after 9 months storage under ambient conditions, Q1S, (c) Q1S after size reduction, $Q1S_{milled}$, (d) quenched griseofulvin, Q2, and (e) raw material, R.

The effect of milling was more pronounced within the first minute. According to IMC (Table 3), the degree of disorder was decreased from 5.3% to 1.3% after 3.4 min milling (RM2), suggesting a deactivation mechanism. This can be due to an increase in the thermal energy of the sample under grinding, with the result that the temperature at the particle surface reaches T_g. Thus, disordered regions of griseofulvin will undergo a phase transition from a glassy to a rubbery state, and the degree of disorder may subsequently be decreased through recrystallization.[22]

The Effect of Quenching on the Solid-State Structure and Solubility

The quenched griseofulvin Q2 sample consisted of glassy brownish yellow masses; Q1 was relatively darker than Q2. The glassy appearance of these solids could probably be related to their more disordered structure.

Although the XRPD patterns and the DSC profiles of Q1 and Q2 were almost identical (Figs. 4 and 5), the values of enthalpy of crystallization revealed that Q2 was less disordered than Q1 (Table 3). This was in good agreement with the solubility data. The saturation concentration of Q1 (Figs. 7 and 8) was 44 μg/mL, whereas the saturation concentration of Q2 (Fig. 8) was only 19 μg/mL. The higher solubility of Q1 compared to Q2 is probably explained by a higher general degree of disorder (Table 3), and reactivity, in Q1 than in Q2. This difference may have been caused by differences in the quenching procedure (i.e., the shorter heating time and the longer solidification time for Q2), which could have favored the formation of a less disordered structure.

The collective results of XRPD, DSC, and solubility data thus suggest that Q1 and Q2 could be considered as two different glassy states of griseofulvin, with two different energy levels and reactivity (saturation concentration). According to these results, Q1 is totally disordered and thus this sample is used as the totally amorphous standard (Table 4).

The Effect of Storage on the Solid-State Structure and Solubility Plateau of Amorphous Griseofulvin

As a result of 9 months storage under ambient conditions, the degree of disorder of quenched griseofulvin Q1 dropped from 100% to 83% (DSC data, Table 3) and its saturation concentration (Fig. 8) dropped from 44 to 26 μg/mL. The sample became matte in appearance and its color changed toward

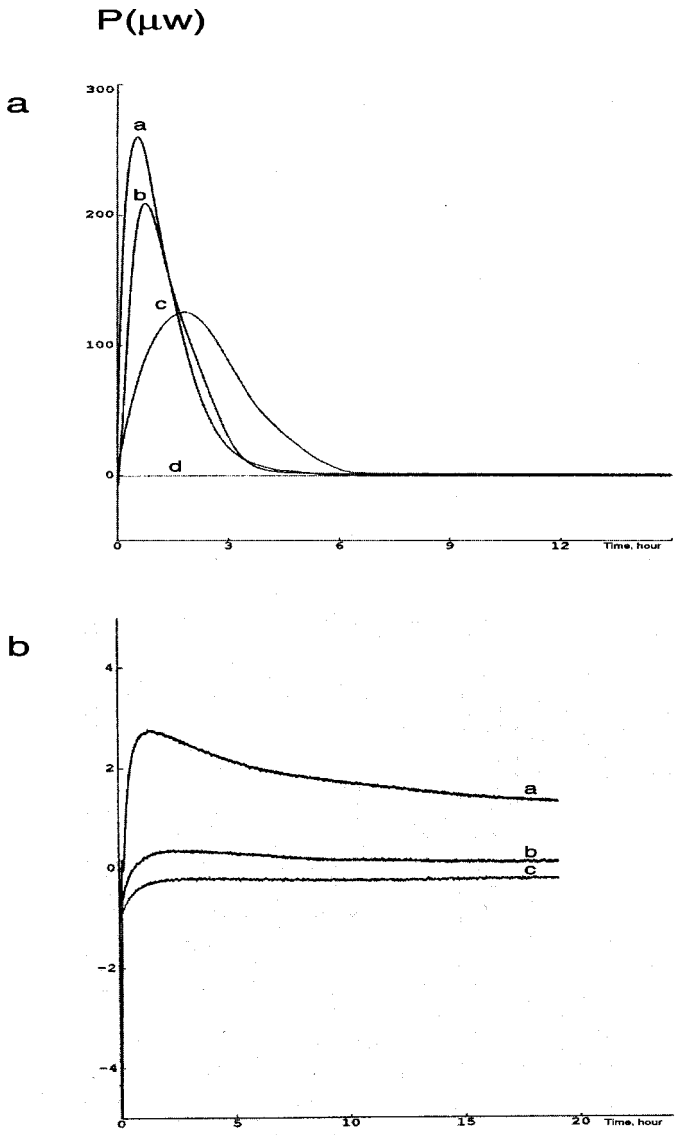

Figure 6. Typical responses obtained for griseofulvin samples exposed to HCl vapor at 25°C, using the isothermal microcalorimeter. Fig. 6a: (a) Q2, (b) $Q1S_{milled}$, (c) Q1S, and (d) R. Fig. 6b: (a) RM1, milled for 1.3 min, (b) RM2, milled for 3.4 min, and (c) R. The area under the curves, i.e., (Q) is listed in Table 2.

Table 4. Summary of solid state structure of test materials.

Material	Model	Solid-state structure
R	One-state	Totally ordered
RM1	Two-state	Ordered core, partially disordered surface
RM2	Two-state	Ordered core, partially disordered surface
Q1	One-state	Totally disordered-Higher energy level
Q2	One-state	Totally disordered/semiordered-Lower energy level
Q1S	Two-state	Disordered core, semiordered surface
$Q1S_{milled}$	Two-state	A mixture of particles with disordered and semi-ordered surfaces, but in general the number of disordered surfaces is increased.

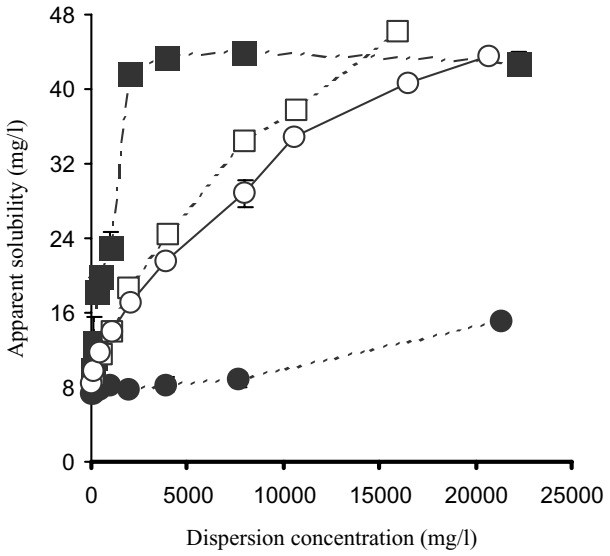

Figure 7. The effect of dispersion concentration on the apparent solubility of different griseofulvin samples at 23°C. Symbols: quenched, Q1, ■; milled for 1.3 min, RM1, □; milled for 3.4 min, RM2, ○; and raw material, R, ● (bars = standard deviation).

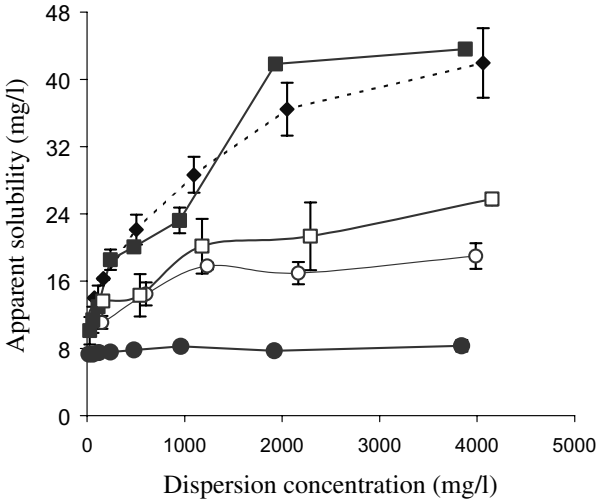

Figure 8. The effect of dispersion concentration on the apparent solubility of different griseofulvin qualities: freshly quenched, Q1, ■; Q1 after 9 months storage under ambient conditions, Q1S, □; freshly quenched, Q2, ○; Q1S after attrition, $Q1S_{milled}$, ◆; and raw material, R, ●, at 23°C (bars = standard deviation).

a light yellow (Table 1). This change in color may have been caused by absorption of moisture[12] by amorphous griseofulvin during storage, resulting in partial surface crystallization. Since the environmental moisture was initially only in contact with the surface of the powder, the color shift was only a surface phenomenon, especially since Q1 consisted of large lumps. The internal core of the particles was still glassy brownish and totally disordered. This was also in good agreement with the SEM pictures (Fig. 2). Thus, it seems that the molecules on the surfaces of the particles are less disordered than those inside, as the recrystallization reaction starts at the surface and moves inward.

Comparison of the results obtained from DSC, XRPD, SEM, and color shift before and after storage of Q1 leads to the conclusion that the material converted to a less disordered state upon storage.

New glassy surfaces were seen when the lumps of Q1S were milled into smaller pieces ($Q1S_{milled}$) after storage. These results are also in agreement with the SEM results (Figs. 2–3). As shown in Fig. 8, the original solubility value of Q1 (44 μg/mL) was regained for $Q1S_{milled}$. Thus, milling caused the reactivity of Q1S to be enhanced further. The effect of milling here is probably more that the coarse amorphous particles (which after storage at ambient conditions were more ordered on the surface) were broken into smaller units, exposing the intact disordered domains in the particle core. This was assumed to be due to the creation of a large number of small particles with totally disordered surfaces.

This result is of particular importance for stability problems and dissolution problems associated with the reaction between amorphous solids and moisture. This means that if such a reaction is in its initial stage (i.e., limited to a thin surface layer), a gentle attrition process can change the exposed surface to obtain dissolution behavior similar to that of the original solid (i.e., Q1 in this case).

The Apparent Solubility in Systems Containing Physical Mixtures of Crystalline and Amorphous Griseofulvin

In order to study the effect of the presence of different amounts of crystalline particles on the dissolution kinetics and thus on the apparent solubility of Q1S, changes in the concentration of this sample were also studied in the presence of griseofulvin crystals after the same stirring times. Thus, a two-state system was established by mixing known ratios of crystalline griseofulvin and Q1S. The monitored apparent solubility values in suspensions containing these mixtures are compared with the apparent solubility values for Q1S and Q1 at the corresponding

dispersion concentrations, in the absence of crystalline particles in Fig. 9.

According to previous results, there is no difference in the solubility of crystalline grisoefulvin after 5 and 24 h stirring.[38] The results of the present study (Fig. 9) also indicate that the solubility values of both crystalline griseofulvin (0% disorder) and Q1S (83% disorder) were constant after 3 and 24 h stirring, when measured separately and independently. Thus, in both cases the saturation level is reached within 3 hours. After 3 h stirring, the apparent solubility values in all suspensions containing mixtures of Q1S and griseofulvin crystals were very close to the apparent solubility value of Q1S (Fig. 9).

However, after 24 h stirring in the suspension containing 43% disorder, the solubility increased significantly, approaching that of Q1. It would appear that because of the relatively low proportion of Q1S particles, the entire semiordered surface of Q1S particles was gradually dissolved until, after 24 h dissolution and stirring, only the totally disordered particle core remained. As explained above, the internal core of Q1S is in fact similar to the whole Q1 structure. Thus, a new equilibrium was established between the totally disordered phase and the surrounding liquid, resulting in an increase in the apparent solubility, until the solution was saturated with respect to Q1.

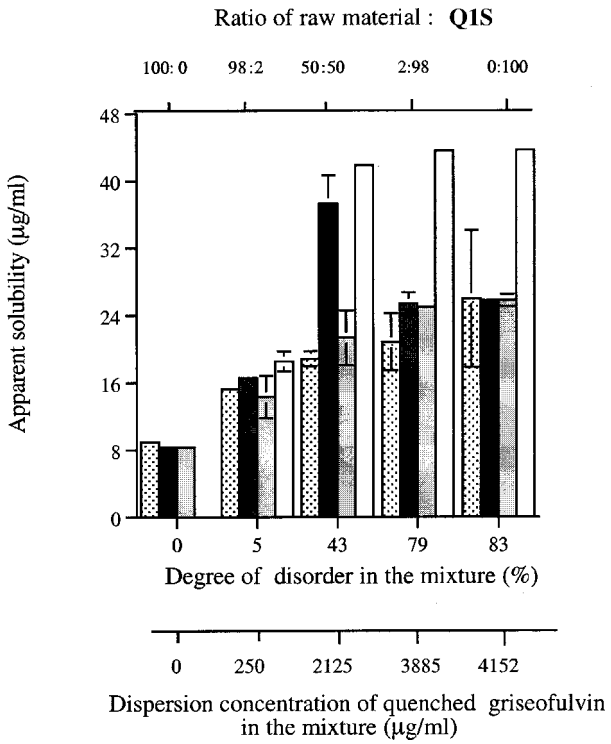

Figure 9. The apparent solubility of griseofulvin as a function of degree of disorder in the mixture, using a two-state model (i.e., physical mixtures of amorphous and crystalline griseofulvin) after 3 h (dotted) and 24 h (black) stirring under ambient conditions (bars = standard deviations); Q1S in the absence of crystals: grey; Q1 in the absence of crystals: white (24 h stirring).

The same explanation can be applied to the dissolution behavior in the suspension that contained 5% disorder, because the same behavior was observed in that suspension (i.e., after 24 h stirring, the apparent solubility was close to that of Q1, at the corresponding dispersion concentration).

In the suspension containing 79% disorder, no such increase in apparent solubility was found. The amount of Q1S was so high that it could be expected to stay relatively intact for a considerable period of time without a complete dissolution of the peripheral semiordered layer.

In earlier studies (Mosharraf, Sebhatu, and Nyström, 1999; Mosharraf and Nyström, 1999), it was suggested that if the solid surface is partly crystalline and partly amorphous the solution will be in equilibrium with both phases and the net apparent solubility will fall between those of the two standards. Consequently, it was suggested that if the external disordered surface layer was discontinuous, the apparent solubility would not approach the saturation level of the totally amorphous structure. However, the results of the present study suggest that, as long as the amount of disordered surfaces in the system is high enough, the apparent solubility will be determined by these more disordered phases. Thus, in a system based on a two-state model, only the disordered parts determine the solubility, unless the amount of disorder is so small that equilibrium with the whole solution is not possible, for instance if only one in 10,000 parts is amorphous (see case B in Fig. 1). In this case the crystalline phase determines the solubility. It can thus be concluded that, in all cases studied, where a two-state system was suggested (Table 4), the apparent solubility of the exposed disordered phase determined the apparent solubility of the mixture.

The Relationship Between Apparent Solubility and Dispersion Concentration

The monitored solubility values of the test materials are plotted vs. the dispersion concentrations in Figs. 7 and 8. It appears that the solubility of crystalline griseofulvin is stable around 8 mg/L within a

wide dispersion concentration range and in general is independent of dispersion concentration. However, at a very high dispersion concentration of 22,000 mg/L (Fig. 7), such a dependency exists and apparent solubility increases to 15 mg/L.

The solubility values of the RM1 and RM2 are significantly dependent on dispersion concentration until at higher dispersion concentrations the saturation concentration of the totally disordered standard (44 mg/L) is reached (Fig. 7). The reason behind this observation is explained by Elamin et al.[20] and Mosharraf, Sebhatu, and Nyström[21] in more detail and seems to be related to the existence of higher absolute amount of disordered surfaces at higher dispersion concentrations. (As larger amounts of material are added to the solvent, the solubility of the drug will increase progressively, and since more disordered material will be available, there is enough disordered structure to establish an equilibrium solubility representative for disordered material.) The same explanation may be used to explain the increase in the solubility of the totally ordered griseofulvin. This increase may be due to minor amounts of impurities or defects[39] in the solid-state structure of the griseofulvin crystals, which seem to become significant only at such high dispersion concentrations.

The solubility of totally disordered/semiordered griseofulvin (i.e., Q1, Q1S, and Q2) initially depends on dispersion concentration; but at specific critical dispersion concentrations, solubility remains stable and is independent of dispersion concentration. These critical dispersion concentrations are reached at 2000 mg/L for Q1 and at approximately 1000 mg/L for Q1S and Q2. The reason for this observation is not clear.

It should be mentioned that the reason the saturation concentration of Q1S and Q2 was studied solely up to a dispersion concentration of 4000 mg/L, was that the plateau of Q1 was reached at a dispersion concentration of 2000 mg/L, and it did not seem necessary to test the solubility of Q1S or Q2 at a very high dispersion concentration of 20,000 mg/L.

The Saturation Concentration Zones and Solubility Values

Comparison of the solubility plateaus shown in Figs. 7 and 8 reveals that generally there are three different solubility zones for the different solid states of griseofulvin. Firstly, the lowest solubility level is that of the crystalline form with a value around 8 mg/L. This solubility level is thermodynamically the most favored. Secondly, the highest solubility plateau occurs at the saturation concentration of the totally disordered form (Q1), at 44 mg/L. (Note that the apparent solubility values of RM1, RM2, and $Q1S_{milled}$ also reached the same plateau level at high dispersion concentrations.) Finally, there is an intermediate solubility plateau, which falls between the other two. The level of this plateau seems to be very close or equal to that of Q2. However, the whole zone which is trapped between these two extremes (i.e., profiles for the totally ordered and totally disordered standards) belongs to partially crystalline solids. If the plateau of the profile falls within this zone, the material is semiordered at the surface, a glass of lower energy, or a combination of the two. The saturation concentrations of Q1S and Q2 (i.e., 26 mg/L and 19 mg/L, respectively) appear to fall within this zone. Thus, in spite of the high degree of disorder in Q1S and Q2 (Table 3), in these cases the solubility plateaus differ significantly from that of the totally disordered sample.

The Relationship Between Degree of Disorder and Minimum Dispersion Concentration to Reach Saturation

As shown in Figs. 7 and 8, the saturation concentration of totally amorphous griseofulvin (Q1) in RM1 and RM2 suspensions is reached at dispersion concentrations of approximately 15,000 and 20,000 mg/L, respectively. The same saturation concentration was reached in the Q1 suspension at a dispersion concentration of 2000 mg/L. It is then concluded that the energy level of the disordered state in these samples (i.e., RM1, RM2, and Q1) is the same (i.e., they all contain the same kind of high-energy amorphous phase). The difference is instead related to how much of this amorphous phase exists in each material.

As shown in Fig. 10, the limited number of data points indicates a possible linear relationship between the degree of disorder obtained by IMC (for RM1, RM2, Q1, and $Q1S_{milled}$) and the minimum dispersion concentration required in the corresponding suspension in order to reach the saturation concentration plateau of the totally disordered structure (Q1). The greater the degree of disorder, the lower is the amount required. This is also in good agreement with earlier data.[21]

This indicates that solubility measurements of this kind are very sensitive to small variations in surface disorder. Thus, the proposed solubility model

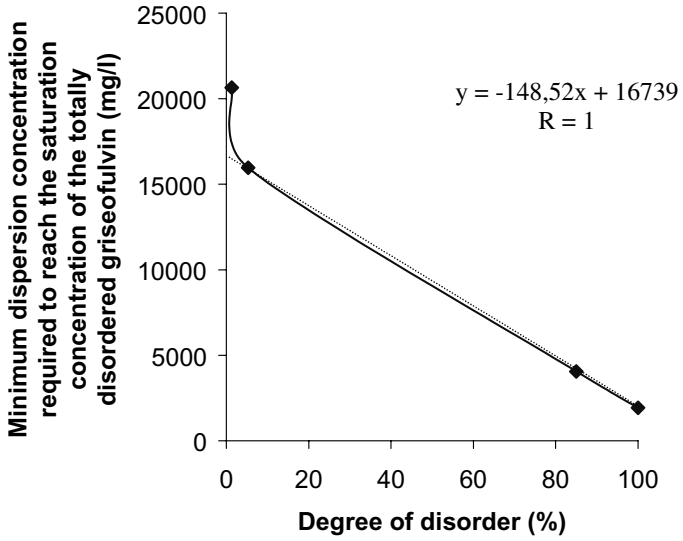

Figure 10. The relationship between the minimum dispersion concentration required to reach the saturation concentration of the totally disordered griseofulvin and degree of disorder obtained by IMC. The dotted line shows the linear regression of the linear part of the diagram.

can be used as a tool for verifying the existence of solid-state disorder in the test materials. However, in cases where the amount of disorder is very small (e.g., RM2), very large quantities of material are required to reach the saturation level of the totally disordered standard.

The Solubility Model

The results presented in this article confirm earlier findings that different apparent solubility plateaus for a substance can exist. They also confirm the suggestion that the plateaus differ according to the degree of disorder at the surface of the particle in equilibrium with the solvent.

Thus, different situations may occur. These situations are illustrated in a schematic model in Fig. 11.1) The surface is completely and homogeneously ordered, which could be the case for a totally ordered structure (case A) or an almost totally ordered structure (case B); 2) The surface is completely and homogeneously disordered, which could be the case for a totally disordered structure (case H), an almost totally disordered structure (case G), or for a structure where the internal core is ordered (case D); 3) The surface is homogeneously in a less ordered state, but is not completely disordered, i.e., the surface is semiordered, which could be the case for a totally semiordered structure (case E), a structure with a semiordered surface but with a totally disordered core (case I), or a totally crystalline core (case C); 4) The surface is a heterogeneous mixture of more ordered and less ordered phases (two state system on the surface) (case K in Fig. 11). It should be noted that in such cases the energy levels of the disordered parts might also vary.

Thus, when the solid has a semiordered character, the saturation concentration never reaches the solubility plateau of the amorphous material, but stops at an intermediate level.

If the surface is a heterogeneous mixture of more ordered and less ordered phases, which are distinguishable, the solubility of the disordered phases determines the solubility of the system. If these disordered parts have high intrinsic energy (are completely disordered), the plateau value of the totally disordered standard will be reached at high dispersion concentrations, even if the surface contains crystalline phases (Fig. 11, case K). If these disordered parts are in a lower energy state than the totally disordered phases, the plateau will be intermediate and determined by the energy state and reactivity of these sites, but it will show a concentration-dependent profile before the plateau is reached.

On the other hand, if the sample is a glass polyamorph with a lower energy state or is totally semiordered (Q2), the plateau also falls in the intermediate zone but is relatively independent of the dispersion concentration (Fig. 11, case E).

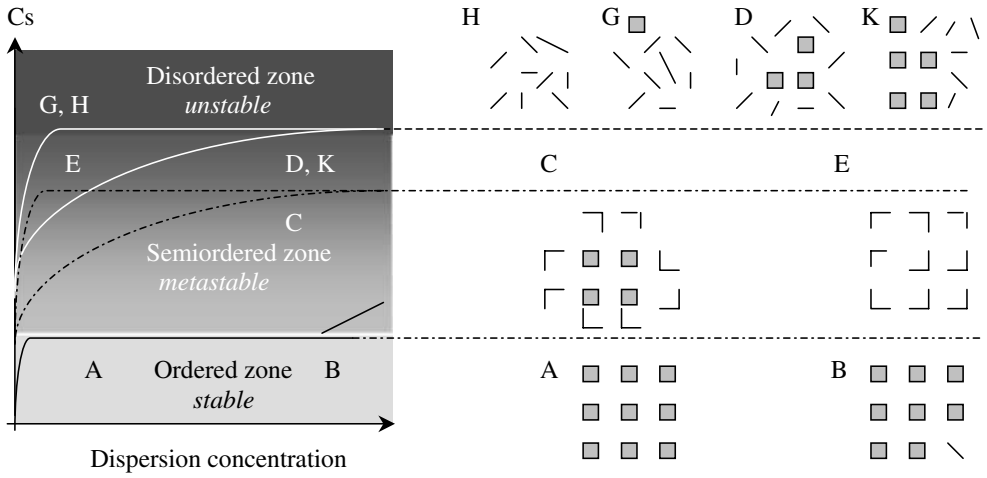

Figure 11. Solubility profiles of a drug with a disordered, semiordered, or ordered solid-state structure, as a function of dispersion concentration of solid drug. A and H are totally ordered and totally disordered standards. B is a crystal with minor amounts of defects or impurities. G is a disordered structure with minor crystalline components. E is a totally semiordered solid (one-component state). C is a solid with semiordered surface but a crystalline core. D is a solid with a totally disordered surface and an ordered (crystalline) core. K is a solid in which the totally ordered and totally disordered parts coexist (a two-component state, i.e., the structure is not semiordered). This form is not included in Fig. 1. In this figure, only those cases that have been studied in this article are considered (i.e., cases F, I, and J, illustrated in Fig. 1, are not considered here). C_s is the saturation concentration of drug.

The Stability of Metastable Solutions of Griseofulvin in the Absence of Solid Phase

It is known that in a suspension there is a metastable equilibrium between the disordered surface and the solution. As long as this equilibrium exists, the saturation concentration will remain at the same level. However, as soon as the solid particles are removed from the solution by centrifugation or filtration, the basis for the equilibrium is removed. It would be expected that under such circumstances, the concentration of solute in the solution would fall rapidly. However, as shown in Fig. 12, the metastable solutions of griseofulvin were stable over a 50-day period in the absence of the solid phase. Similar observations were reported by Phillips and Byron,[19] who showed that despite apparent supersaturation, there was no evidence for any crystal growth in supersaturated solutions of methylprednisolone over a 120-day period.

These behaviors may be explained through consideration of the crystal growth and phase separation mechanisms. It is known that nucleation and growth, cluster formation, concentration fluctuation, and reduction in diffusivity are phenomena that occur in supersaturated solutions.[40] It has also been pointed out that if at least one group in the molecule is able to act as both a proton donor and a proton acceptor (for example, OH− or an amino-group), intermolecular H-bonds are formed and molecular aggregation may occur. It is believed that self-association of organic solutes such as phenols affects their solubility behavior in all solvents.[41] It seems, thus, probable that when the solid phase is removed from the solution, the hydrophobic solute molecules will self-associate to reduce the free energy of the system. Hydrophobic bonding between monomers, which leads to formation of more complex aggregates, seems to be a key factor.

In the absence of crystals and foreign particles, nucleation is controlled by homogeneous nucleation.[36] In the case of griseofulvin, there was no crystal growth occurring in the system during the test period (Fig. 12), indicating that the supersaturated solutions of griseofulvin tested (with $C_{Q1S}/C_{crystal}$ values of 2–3) are metastable. Thus, it is possible that precipitation and phase separation are inhibited as a result of molecular aggregation, self association, and cluster formation. Consequently, these molecular aggregates cause the supersaturated solution to approach a metastable equilibrium.

At concentrations higher than those in the metastable region, a supersaturated solution is unstable, and phase separation occurs.[42]

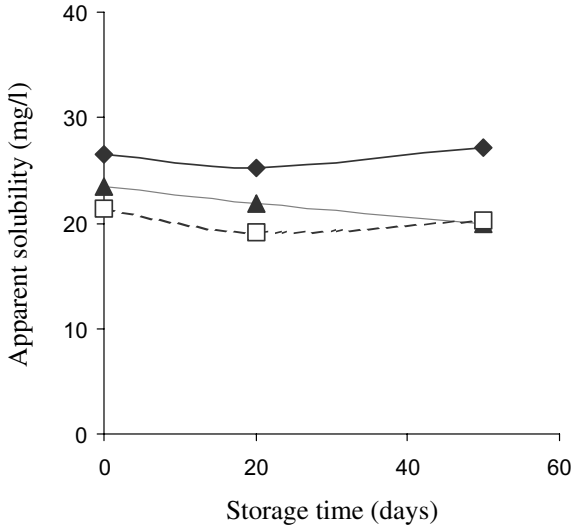

Figure 12. Stability of metastable solutions of Q1S over time and under ambient conditions, in the absence of solid phase. The dispersion concentrations are 1228, ▲ 2290, □, and 4224, ◆.

CONCLUSIONS

It was confirmed in this article that in partially crystalline systems, the saturation concentration is an interfacial phenomenon, which depends on the amount, reactivity, and solid-state structure of the exposed solid surfaces in equilibrium with solution.

The solubility model described by Mosharraf, Sebhatu, and Nyström[21] was refined to consider the solubility behavior of drugs in both one-state and two-state systems.

From the results of the present study and earlier studies (21 and 22), it is suggested that in a plot of apparent solubility vs. dispersion concentrations, there are at least three main plateaus for several drugs in which the solid-state structure is energetically homogeneous and based on the one-state model: 1) The saturation level of a totally crystalline solid, which has the lowest solubility level and falls in a thermodynamically stable zone; 2) The saturation level of a totally amorphous solid, which has the highest solubility level; 3) The saturation level of a totally semiordered solid, which falls between the other two.

In all three cases, the solubility of the solid seems to be relatively independent of the amount of drug added, provided the concentration exceeds specific threshold values (i.e., 1000 mg/L for Q2 and 2000 mg/L for Q1).

Any deviation from these plateaus is indicative of the existence of heterogeneity of energy levels in the solids, i.e., a two-state system. In such cases, the apparent solubility will be strongly related to the dispersion concentration, until at high additions the saturation concentration of the disordered or semiordered phase is reached.

In a two-state system, the solubility of the disordered/semiordered phase determines the solubility of the system, as long as the amount of disordered/semiordered solid phases in the dispersion is in excess.

The proposed solubility model can be used as a tool for the qualitative verification of the existence of solid-state disorder on the surface of particles of test materials. The sensitivity of this method seems to be extremely high and comparable with methods such as isothermal microcalorimetry.

The obtained supersaturated solutions with a concentration around 20–26 mg/L are metastable over a 50-day period. It is suggested that the stability of these solutions is related to molecular self-association after solid-phase separation**.** Slower diffusivity in metastable solutions inhibits the crystal growth mechanism.[40]

Additionally, a method for the determination of the solid-state structure of hydrophobic sparingly water-soluble drugs was developed using HCl vapor as the reacting phase in isothermal microcalorimetry.

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REFERENCES

1. Corrigan, O.I.; Holohan, E.M.; Sabra, K. Amorphous forms of thiazide diuretics prepared by spray drying. Int. J. Pharm. **1984**, *18*, 195–200.
2. Yamaguchi, T.; Nishimura, M.; Okamoto, R.; Takeuchi, T.; Yamamoto, K. Glass formation of 4″-*O*-(4-methoxyphenyl) acetyltylosin and physicochemical stability of the amorphous solid. Int. J. Pharm. **1992**, *85*, 87–96.
3. Matsuda, Y.; Otsuka, M.; Onoe, M.; Tatuism, E. Amorphism and Physicochemical stability of lspray-dried frusemide. J. Pharm. Pharmacol. **1992**, *44*, 627–633.

4. Frömming, K.H.; Grote, U.; Lange, A.; Hosemann, R. Freeze-dried formulations of griseofulvin. Part 1. Preparation, properties and in vitro drug release. Pharm. Ind. **1986**, *48*, 283–288.
5. Lehto, V.; Laine, E. A kinetic study on crystallisation of an amorphous lubricant. Pharm. Res. **1997**, *14*, 899–903.
6. Gubskaya, A.V.; Lisnyak, Y.V.; Blagoy, Y.P. Effect of cryogrinding on physico-chemical properties of drugs. I. Theophylline: Evaluation of particles sizes and the degree of crystallinity, relation to dissolution parameters. Drug Dev. Ind. Pharm. **1995**, *21*, 1953–1964.
7. Ward, G.H.; Schultz, R.K. Process-induced crystallinity changes in albuterol and its effect on powder physical stability. Pharm. Res. **1995**, *12*, 773–779.
8. Shalaev, E.Y.; Shalaeva, M.; Byrn, S.R.; Zografi, G. Effects of processing on the solid-state methyl transfer of tetraglycine methyl ester. Int. J. Pharm. **1997**, *152*, 75–88.
9. Frömming, K.H.; Kreuschner, K.; Hosemann, R.; Hasse, J. Stability of Pheylbutazone and griseofulvin in solidified melts with urea. Acta. Pharm. Technol. **1980**, *26*, 69–73.
10. Hüttenrauch, R. New concepts in pharmaceutics. Labo-Pharma. Probl. Tech. **1983**, *31*, 644–655.
11. Hancock, B.C.; Zografi, G. Characteristics and significances of the amorphous state in pharmaceutical systems. J. Pharm. Sci. **1997**, *86*, 1–11.
12. Ahlneck, C.; Zeografi, G. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid-state. Int. J. Pharm. **1990**, *62*, 87–95.
13. Shalaev, E.Y.; Zografi, G. How does residual water affect the solid-state degradation of drugs in amorphous state. J. Pharm. Sci. **1996**, *85*, 1137–1141.
14. Byrn, S.A.S. Solid state chemistry—Regulations and Reactions. Proceedings the Int. Symp., New approaches in Pharmaceutical development, organized by Molecular Simulation Inc and Silicon Graphics Computer Systems, San Diego, Feb 19–20, 1998.
15. Suryanarayanan, R.; Mitchell, A.G. Evaluation of two concepts of crystallinity using calcium gluceptate as a model compound. Int. J. Pharm. **1985**, *24*, 1–17.
16. Hüttenrauch, R. Molecular Pharmaceutics as a basis of modern pharmaceutical technology. Acta Pharm. Technol. APV Informationsdienst Suppl. **1978**, *6*, 55–127.
17. Kawashima, Y.; Saito, M.; Takenaka, H. Improvement of solubility and dissolution rate of poorly water-soluble salicylic acid by a spray-drying technique. J. Pharm. Pharmac. **1974**, *27*, 1–5.
18. Kai, T.; Akiyama, Y.; Nomura, S.; Sato, M. Oral absorption improvement of poorly soluble drug using solid dispersion technique. Chem. Pharm. Bull. **1996**, *44*, 568–571.
19. Phillips, E.; Byron, P. Surfactant promoted crystal growth of micronized methylprednisolone in trichloromonofluoromethane. Int. J. Pharm. **1994**, *110*, 9–19.
20. Elamin, A.A.; Ahlneck, C.; Alderborn, G.; Nyström, C. Increased metastable solubility of milled griseofulvin, depending on the formation of a disordered surface structure. Int. J. Pharm. **1994,** *111*, 159–170.
21. Mosharraf, M.; Sebhatu, T.; Nyström, C. The effects of disordered structure on solubility and dissolution rates of hydrophilic, sparingly soluble drugs. Int. J. Pharm. **1999**, *177*, 29–51.
22. Mosharraf, M.; Nyström, C. The effect of dry mixing on the apparent solubility of hydrophobic, sparingly soluble drugs. Eur. J. Pharm, Sci. **1999**, *9*, 147–156.
23. Dialer, K.; Kuessner, K. Surface area generation and energy uptake during oscillating milling of refined sugar; influence of bonding on extreme size reduction. Kolloid-S.S. Polymer **1973**, *251*, 710–715.
24. Chow, K.Y. Crystal modification of griseofulvin using interacting solvents, n-alkanoic acids. Ph. D. Thesis, University of Toronto: Canada, 1989; 145–147.
25. York, P.; Ticehurst, M.D.; Osborn, J.C.; Roberts, R.J.; Rowe, R.C. Characterisation of the surface energetics of milled d1-propranolol hydrochloride using inverse gas chromotography and molecular modelling. Int. J. Pharm. **1998**, *174*, 179–186.
26. Clarkson, J.R.; Price, T.J.; Adams, C.J. Role of metastable phases in the spontaneous precipitation of calcium carbonate. J. Chem. Soc. Faraday Trans. **1992**, *88* (2), 243–249.
27. Cardew, P.T.; Davey, R.J. The kinetics of solvent-mediated phase transitions. Proc. R. Soc. Lond. **1985**, *A398*, 415–428.
28. Rodriguez-Hornedo, N.; Lechuga-Ballesteros, D.; Wu, H.J. Phase transition and heterogenous/epitaxial nucleation of hydrated and

anhydrous theophylline crystals. Int. J. Pharm. **1992**, *85*, 149–162.
29. Mosharraf, M.; Nyström, C. The effect of particle size and shape on the surface specific dissolution rate of microsized, practically insoluble drugs. Int. J. Pharm. **1995a**, *122*, 35–47.
30. Sebhatue, T.; Angberg, M.; Ahlneck, C. Assessment of the degree of disorder in crystalline solid by isothermal microcalorimetry. Int. J. Pharm. **1994**, *104*, 135–144.
31. Grant, D.J.H,; Chow, K.Y.; Lam, S. Relationships between the solid state properties of griseofulvin obtained from different sources and crystallized under various conditions. Proc. 4th Int. Conf. Pharm. Technol., Paris, 1986; Vol. 1, pp. 23–32.
32. Grosvenor, M.P.; Staniforth, J.N. The effect of molecular weight on the rheological and tensile properties of poly (β-caprolactone). Int. J. Pharm. **1996**, *135*, 103–109.
33. Angberg, M.; Nyström, C.; Castensson, S. Evaluation of isothermal heat-conduction microcalorimetry in pharmaceutical stability studies. V. A new approach for continuous measurements in abundant water vapour. Int. J. Pharm. **1992**, *81*, 153–167.
34. Ahmed, H.; Buckton, G.; Rawlins, D.A. The use of isothermal microcalorimetry in the study of small degrees of amorphous content of a hydrophobic powder. Int. J. Pharm. **1996**, *130*, 195–201.
35. Stephenson, G.A.; Borchardt, T.B.; Byrn, S.R.; Bowyer, J.; Bunnell, C.A.; Snorek, S.V.; Yu, L. Conformational and color polymorphism of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile. J.Pharm. Sci. **1995**, *84*, 1385–1386.
36. Mershmann, A. Supersaturation and nucleation. Trans IchemE **1996**, *74*, *Part A*, 812–820.
37. York, P. Solid state properties of powders in the formulation and processing of solid dosage forms. Int. J. Pharm. **1983**, *14*, 1–28.
38. Mosharraf, M.; Nyström, C. Solubility characterization of practically insoluble drugs using the Coulter counter principle. Int. J. Pharm. **1995b**, *122*, 57–67.
39. Higuchi, T.; Shih, F.L.; Kimura, T.; Rytting, J.H. Solubility determination of barely aqueous-soluble organic solids. J. Pharm. Sci. **1979**, *68*, 1267–1272.
40. Myerson,A.S.ThermodynamicandSpectroscopic Studies of Supersaturated Solutions. Proceedings the Int. Symp., New approaches in Pharmaceutical development, organized by Molecular Simulation Inc and Silicon Graphics Computer Systems, San Diego, Feb 19–20, 1998.
41. Grant, D.J.W.; Higuchi, T. Solubility behavior of organic compounds. *Techniques of Chemistry*; John Wiley & sons: New York, 1990; Vol. 21, 234–305.
42. Myerson, A.S.; Lo, P.Y. Cluster formation and diffusion in supersaturated binary and ternary amino acid solutions. J. Cryst. Growth, **1991**, *110*, 26–33.